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Original Research Article

Adverse Effects of Oral Hypoglycemic Agents and Adherence to them among Patients with Type 2 Diabetes Mellitus in Nepal

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ABSTRACT:

Introduction: Oral hypoglycemic agents (OHAs) are the most common drugs used in Type 2 Diabetes Mellitus. There are various established adverse effects related to their use including hypoglycemia, weight gain, gastrointestinal disturbance, lactic acidosis, and fluid retention. However, the pattern of adverse effects related to OHAs in Nepalese patients still needs to be explored. Our study aims to determine the pattern of adverse effects resulting from the use of OHAs among Type 2 Diabetes mellitus patients and their adherence to the medication. **Methods**: All diabetic patients who met the inclusion criteria were enrolled in the study. After informed consent, patients were interviewed and evaluated as per the designed proforma. They were mainly studied for common drug used, adverse effects of the drugs, occurrence of hypoglycemia, and adherence to treatment. **Results**: The study comprised of 183 patients with mean age of 58.73 years (*SD* = 12.95). Fifty-six (30.6%) patients said that they developed adverse effects of drugs but only 21 (11.5%) of them reported to their treating physician. Most common adverse effect were related to central nervous system such as tingling sensation of hands and feet, dizziness, drowsiness, etc. Though 91 (49.7%) patients had developed symptoms suggestive of hypoglycemia, only 31 (16.9%) knew that it was due to hypoglycemia. Majority of the patients ($n = 143$, 78.1%) administered the drugs as prescribed by the physician. Among the defaulters, the most important reasons for failure to properly administer the drugs was forgetfulness in 82.5% ($n = 33$, $N = 40$) of cases. Among the study variables family history of chronic illness ($p = 0.046$) and information about adverse effects from physician ($p = 0.001$) had a significant relationship with incidence of adverse effects. Whereas none of them had a significant relationship with adherence to hypoglycemic medication. **Conclusion**: The incidence of adverse effects was high with hypoglycemia occurring in 49.7% of the cases, though only one-third of them recognized it to be due to hypoglycemia, in the patients with Type 2 Diabetes Mellitus. Family history of chronic illness and information about adverse effects from the physician had significant relationship with the incidence of adverse effects of hypoglycemic treatment.

Keywords: adverse effects • type 2 diabetes mellitus • hypoglycemia • hypoglycemic agents • patient adherence

INTRODUCTION:

Diabetes mellitus (DM) is a group of metabolic disorders sharing the common underlying feature of hyperglycemia. Hyperglycemia in DM results from defects in insulin secretion, insulin action, or most commonly, both. The chronic hyperglycemia and metabolic dysregulation may be associated with secondary damage in multiple organ system, especially the kidney, eyes, nerves and blood vessels.[1] DM has evolved as a global health issue, probably due to change in life style,

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population growth, increasing prevalence of obesity and inactivity, which is estimated to affect at least 300 million people worldwide by 2025.[2] The condition can be classified into two types Type 1 and Type 2 DM (T2DM) based on its etiopathogenic and pathophysiological mechanism. Patients with T2DM require medical treatment throughout their life; also, they need to maintain proper diet and physical activity in order to maintain the sugar level.[3] Different factors are responsible for the adverse effects during medication. Also, people do not have much idea about the management of the sudden adverse effects occurring during the medication. In Nepal, there is no compulsory law necessitating drug manufacturers to submit safety data from the Nepalese population prior to approval of the medicines.[4] Inability to maintain adherence to treatment regimens, dietary modifications, and lifestyle changes has been major cause of failure of diabetes management. Our study aims to analyze and describe the patterns of adverse effects associated with the use of oral hypoglycemic agents, adherence to the medication, and factors affecting them.

METHODS:

A cross sectional analytical study was conducted among 183 Type 2 diabetic patients attending Dhulikhel Hospital (Kathmandu University Hospital) and other diabetic clinics in Kavre district and Kathmandu Valley, from February 2014 to October 2014. Patients of all age and sex who were diagnosed with T2DM, on treatment either admitted or who came for the regular checkup were included in this study. The individuals under other medications along with anti-diabetic treatment, as well as those with other disorders along with T2DM were also included. Patients who refused to consent to the study were excluded from the study.

The topic was reviewed and ethical approval was granted by Institutional Review Committee of Kathmandu University School of Medical Sciences (IRC-KUSMS) under protocol approval number 35/14. The target population meeting the inclusion criteria were enrolled in the study and after receiving consent, they were interviewed using the preformed structured questionnaire. The data information included personal history, dietary habits, physical activity, drugs administered and adverse effects seen. Additional information regarding blood sugar level at the time of diagnosis and its recent value, other concomitant diseases, occurrence of hypoglycemia were included. The data collected were tabulated in MS Excel 2007 and were analyzed by IBM SPSS Version 16.0. Continuous variables were expressed in terms of mean and standard deviation (*SD*) while categorical variables were expressed in terms of frequency and percentages. Association between categorical variables with adherence status and incidence of adverse effects were calculated using Pearson *Chi-squared* test and *Fisher exact* test depending upon number of expected value within cells of table. *P* value less than 0.05 was considered significant.

RESULTS:

The study comprised of 183 patients with Type 2 diabetes mellitus (T2DM). There were 116 (63.4%) males and 67 (36.6%) females. The mean age of patients was 58.73 years (*SD* = 12.95) Mean Body Mass Index (BMI) was 23.83 kg/m2 (*SD* = 3.95). There were 87 (47.5%) literate and 96 (52.5%) illiterate people. Among all, 119 (65%) patients used to perform regular exercise. Among those who exercised, 78.2% (*n* = 93, *N* = 119) had controlled blood sugar level.

Metformin alone was used by 91 (49.7%) cases, whereas 24 (13.2%) consumed other oral hypoglycemic drugs (sulfonylurea/ Dipeptidyl peptidase 4 inhibitors/ α-glucosidase inhibitors/ thiazolidinedione), 46 (25.1%) consumed combination of metformin and other oral hypoglycemic drugs, 15 (8.2%) used insulin alone, and seven (3.8%) used metformin and insulin. Among all, 77 (42.1%) patients used only anti-diabetic drugs whereas others took combination of anti-diabetic and other non-diabetic drugs. These non-diabetic drugs included anti-hypertensive agents, statins, vitamins, cephalosporins, etc.

The study revealed that, among 183 patients, 56 (30.6%) patients reported adverse effects. Among 56 patients, 31 (55.6%) said they experienced hypoglycemia, eight (14.3%) had tingling sensation of hands and feet, six (10.7%) patients each reported dizziness and gastrointestinal symptoms, and five (8.9%) developed other adverse effects like body ache, fatigue, joint pain, and eye irritation. Of all patients who developed adverse effects, only 21 (37.5%) reported about them to their treating physician.

When patients were first explained about the

symptoms of hypoglycemia and then asked again whether they had experienced such symptoms, 91 (49.7%) of them agreed that they had such symptoms. This showed that 60 (65.9%, *N* = 91) patients who were taking drugs for diabetes did not even know the features of hypoglycemia. Only 11 (6%) of the total patients were informed about the adverse effects of the oral hypoglycemic drugs by their treating physician.

Majority of the patients (*n* = 143, 78.1%) administered the drugs as per the physician's recommendation. Among the individuals who did not follow the physician's recommendation on drug consumption, most of them (*n* = 33, *N* = 40, 82%) said it was due to forgetfulness, six (15%) due to carelessness, and mere one (3%) due to financial problems.

According to the American Diabetes Association, the blood sugar level of the diabetic patients must be monitored in every three months with the assessment of glycated hemoglobin (HbA1c).[5] The study defines a patient to be aware if s/he goes for regular checkup of blood sugar level at the interval of three months or less than that. Among the studied patients, 79.24% (*n* = 145) of them were found to be aware.

Association between various variable and adherence to oral hypoglycemic agents is shown in Table 1. There was no significant association of adherence to oral hypoglycemic agents with any of the variables.

Relationship between occurrence of adverse effects and various variables is shown in Table 2. Family history of chronic illness and information about adverse effect from physician had significant relationship with the occurrence of adverse effects. Patients with family history of chronic illness were more likely to have experienced adverse effects of hypoglycemic medication compared to those without family history of chronic illness. Similarly, patients who received information about adverse effects of drugs from physicians were more likely to have experienced adverse effects of hypoglycemic medication as compared to those not receiving information about adverse effects. None of the other variables had significant relationship with occurrence of adverse effects.

Table 1*: Association between various variables and medication adherence*

Variables	Adherent *n (%)*	Non Adherent *n (%)*	X^2	*df*	*p*
Sex					
Male	87(75.0)	29(25)	0.75	1	0.39
Female	54(80.6)	13(19.4)			
Literacy Status					
Literate	70(76.1)	22(23.9)	0.1	1	0.76
Illiterate	71(78.0)	20(22.0)			
Marital Status#					
Unmarried	3(75.0)	1(25.0)			
Married	119(76.3)	37(23.7)	0.6#		0.97
Widow	11(84.6)	2(15.4)			
Widower	8(80.0)	2(20.0)			
Status of Employment					
Unemployed	76(81.7)	17(18.3)	2.3	1	0.13
Employed	65(72.2)	25(27.8)			
Drinking status					
Non Drinker	97(77.0)	29(23.0)			
Drinker	24(75.0)	8(25.0)	0.2		0.93
Past Drinker	20(80.0)	5(20.0)			
Dietary Habits					
Vegeterian	20(90.9)	2(9.1)	2.7	1	0.1
Non Vegeterian	121(75.2)	40(24.8)			
Family History of Chronic Illness					
Yes	62(78.5)	17(21.5)	0.16	1	0.69
No	79(76.0)	25(24.0)			
Practice of Exercise					
Yes	98(79.0)	26(21.0)	0.86	1	0.36
No	43(72.9)	16(27.1)			
Information about adverse effect from Physician					
Yes	11(78.6)	3(21.4)	0.02	1	0.89
No	130(76.9)	39(23.1)			
Concomitant Disease					
Present	80(82.0)	18(18.0)	3.06	1	0.08
Absent	59(71.1)	24(28.9)			
Awareness on the condition					
Yes	111(79.3)	29(20.7)	1.69	1	0.19
No	30(69.8)	13(30.2)			

#Fisher's Exact Test performed

DISCUSSION:

The incidence of type 2 Diabetes mellitus (DM) was found to be more in male population as compared to female population. This result was similar to result of other studies done in different countries where prevalence of type 2 DM was less in female as compared to male.[6] This might be due to more sedentary lifestyle in male, resulting in increased obesity. Moreover, Body fat distribution differs with the sex, where higher proportion of visceral and hepatic fat compartments in male are associated with insulin resistance.[6] Whereas, in

Table 2: Association between various variables and incidence of adverse effects

Variables	Adverse Effect n (%)	No Adverse Effect n (%)	$\chi 2$	df	p
Sex					
Male	22(32.8)	45(67.2)	0.25	1	0.62
Female	34(29.3)	82(70.7)			
Literacy Status					
Literate	26(28.6)	65(71.4)	0.35	1	0.56
Illiterate	30(32.6)	62(67.4)			
Marital Status#					
Unmarried	0(0.0)	4(100.0)	1.85#		0.62
Married	50(32.1)	106(67.9)			
Widow	4(30.8)	9(69.2)			
Widower	2(20.0)	8(80.0)			
Status of Employment					
Unemployed	32(34.4)	61(65.6)	1.29	1	0.26
Employed	24(26.7)	66(73.3)			
Drinking status					
Non Drinker	40(31.7)	86(68.3)	0.57	2	0.75
Drinker	8(25.0)	24(75.0)			
Past Drinker	8(32.0)	17(68.0)			
Dietary Habits					
Vegetarian	8(36.4)	14(63.6)	0.39	1	0.53
Non Vegetarian	48(29.8)	113(70.2)			
Family History of Chronic Illness					
Yes	18(22.8)	61(77.2)	3.99	1	0.046*
No	38(36.5)	66(63.5)			
Practice of Exercise					
Yes	35(28.2)	89(71.8)	1.02	1	0.31
No	21(35.6)	38(64.4)			
Information about adverse effect from Physician					
Yes	10(71.4)	4(28.6)	11.9	1	0.001*
No	46(27.2)	123(72.8)			
Concomitant Disease					
Present	34(34.0)	66(66.0)	1.2	1	0.27
Absent	22(26.5)	61(73.5)			
Awareness on the condition					
Yes	43(30.7)	97(69.3)	0.004	1	0.95
No	13(30.2)	30(69.8)			

#Fisher's Exact test performed *statistically significant

female, there is more subcutaneous and peripheral fat, which is associated with insulin sensitivity and are protective against Type 2 Diabetes. This make female less susceptible to Type 2 Diabetes than their male counterparts, who suffer from diabetes at lower mass index than female.

Analysis of the T2DM patients showed almost equal percentage of literate and illiterate participants in our study. This may be due to the fact that even if the patients are illiterate, they may have proper diabetic knowledge. This is supported by study done in USA where there was no direct association of glycemic control with literacy but association was seen with diabetic knowledge.[7] In our study, among 119 patients who performed regular exercise, 78.15% of them had controlled blood sugar level. Exercise has shown to protect individuals from developing metabolic syndrome.[8] It reduces insulin resistance that helps in regulation of blood glucose level, lowers uric acid and triglycerides whereas there is increase in the HDL cholesterol ratio.[9]

Polypharmacy was found to be common among the patients. Since patient suffering from T2DM commonly show other concomitant diseases like hypertension, dyslipidemia, polypharmacy is common.[5] Polypharmacy has been often linked with decreased medication adherence is also associated with potential drug interactions and adverse effects.[10] Polypharmacy comprises of multiple drugs with complex drug schedule which are often difficult to be followed by patients which may be the cause of poor adherence.[11] However, reduction in number of drug might cause under treatment, specially in T2DM patients with dyslipidemia, resulting in serious consequences.[10] Thus, pharmacist may have significant role on optimization of the drug and dosage regimen for maximum benefit of patient.

Nearly half (49.7%) of the individuals encountered episodes of hypoglycemia in the study. Among these individuals many of them used metformin with other hypoglycemic agents. This might be the reason for higher incidence of hypoglycemia as in a combination therapy, symptom of hypoglycemia was found to be related to sulfonylureas with no or limited influence of metformin.[12] The patients were also under other medications such as antihypertensive like, statins and other drugs like vitamins, cephalosporins, etc. Use of ACE inhibitor like enalapril has been found to be associated with an increased risk of hypoglycemia.[13] Additionally, a study has shown that concomitant use of amlodipine and telmisartan along with metformin and glimpiride has shown to cause hypoglycemia.[14] As our study comprises patients concomitantly using these drugs with antidiabetic agents, hypoglycemia observed may also be due to these drugs. Even though metformin is mostly used, hypoglycemia is still seen. This may be due to the high incidence of missing of meal. It is supported by a study which reports that missing

or irregular intake of meal is the most frequent behavioral factor causing individual episodes of hypoglycemia.[15] Although people were aware about taking the medication, they were unaware that along with medication proper diet must also be taken.

The study revealed that among 183 patients, 56 (30.6%) of the patients developed various side effects. The major adverse effect was found to be hypoglycemia (n = 31), and other were tingling sensation, dizziness, gastrointestinal disorder like abdominal discomfort, diarrhea, and other effects like fatigue, joint pain and eye irritation. However, when patients were explained about symptoms of hypoglycemia, 49.7% (n = 91) of the patients reported occurrence of those symptoms. This showed that 65.9% (n = 60, N = 91) patients were not aware about the features of hypoglycemia and failed to distinguish symptoms of hypoglycemia as adverse effects. In a study, insulin and the sulfonylureas (SUs) were seen as the main drugs leading to hypoglycemia in patients with T2DM.[16] The major risk factors of hypoglycemia include age where studies have shown that awareness is less common in elderly patients with T2DM. Other risk factors for hypoglycemia include missing meals, coronary artery disease, renal impairment, insulin or sulphonyl urea (SU) treatment, and a history of severe hypoglycemia. Insulin therapy is associated with weight gain and hypoglycemia and shows other adverse effects like local reactions such as swelling, erythema and lipodystrophy, allergy and edema.[17]

Metformin showed adverse effects associated with typically mild, transient and of gastro-intestinal (GI) origin including metallic taste, diarrhea, nausea, vomiting, anorexia and a variety of other GI symptoms such as bloating. Metformin does not induce hypoglycemia; however, the risk of hypoglycemia increases when metformin is used in combination with other therapeutic agents. Continuous use of metformin causes a vitamin B12 deficiency, since it decreases absorption of the vitamin.[18] In a comparative trial, the adverse events like weight gain, hypoglycemia, and GI effects were found to occur more in combination of metformin and glibenclamide as compared to metformin with glimepiride.[19] Other adverse effects reported related to SUs are dermatological effects like rash, purpura and pruritus, GI effects like nausea, vomiting, cholestatic jaundice, and hyperinsulinemia. Study also shows that some patients exerting hypersensitive reactions like allergy to sulfonamide medications may exhibit cross-reactivity with sulfonylureas.[20]

The meglitinides may possess a lower incidence of hypoglycemia and weight gain. A study showed that diarrhoea occurred less frequently and hypoglycemia occurred more frequently but rarely severe with the drug.[21] Hypoglycemia was observed in relatively few thiazolidinediones (TZDs) treated patients, however increased insulin dosing in combination with glitazone resulted in increased risk of hypoglycemia. TZDs have caused increase in body weight and redistribution of adipose tissue from visceral site to subcutaneous regions, so this may cause worsening of existing peripheral edema and can also precipitate or worsen congestive heart failure.[22]

The adverse effects encountered during the therapy may not have been only due to the antidiabetic agents but could have been resulted from the administration of other drugs such as antihypertensive like, statins and other drugs like vitamins, cephalosporins, etc. Angiotensin receptors blockers (ARB) like losartan, telmisartan, etc, β- blocker like metoprolol, ACE inhibitors like enalapril, ramipril, etc and calcium channel blockers like amlodipine. ARB like losartan has been reported to cause side effects like dizziness, lightheadedness, weakness and physical problems including diarrhea, muscle cramp and back or leg pain. These side effects can be misinterpreted as side effects resulted from the antidiabetic agents. The early vasodilating action of the calcium channel blockers have shown to cause effects like headache dizziness, nausea, palpitation and diarrhea.[23]

Our study revealed that only few (n = 40, 21.9%) of the diabetic patients did not follow the medical advice regarding the doses of the drugs. Among those patients, the most common cause of inconstancy was forgetfulness. Similar result was shown by a study where forgetfulness and negligence were found to be the major reasons for inconstancy.[24] Our study comprised more number of elderly patients and people get more forgetful as they age. So, this might be the reason that forgetting behavior of the patient which causes medical inconstancy.

Upon *Chi-squared* analysis, none of the variables that we considered were significantly associated with adherence status. It included factors like awareness on the disease condition, drinking habits, dietary habits, practice of exercise, information

from physician about adverse effects and other non-modifiable variables like sex, literacy status, marital status, employment status, concomitant disease, and family history of chronic illness. Similarly, in other studies as well, sex and education level has not been frequently associated with level of patient adherence.[25,26] Whereas, level of education has been reported to determine adherence status.[27] Though not statistically significant, there are more number of adherent patients who have received information regarding adverse effects from their physicians and are more aware about their condition. Patients are said to have specific mental models while following their treatment regimen and are thus related with adherence.[28] As a result, it is recommended to explore more modifiable factors like health literacy, patient physician interaction, and health perception in relation with adherence.[29]

In case of incidence of adverse effects, information received from the physician regarding adverse effect (p = 0.001) and family history of chronic illness (p = 0.046) were found to be significantly associated with incidence of adverse effects. Other factors were not found to have statistically significant association with incidence of adverse effects. This scenario enhances need for enhancing communication between patient and the physician. Collaborative relationship between patient and physician has been reported to improve patient adherence and thus the clinical outcome.[30] Patients should be given information about what can be done if adverse effects are bothersome in addition to the objective of medication.[31] Causes of adverse effects can often be multifactorial and genetics of a patient among the foremost.[32] In our study, family history of chronic illness seems to have indirect association with incidence of adverse effects may be due to the common gene pool within a family having history of chronic illness.

The study was a cross-sectional and was limited only to small area. It also shared several limitations as patients' compliance was determined only by few parameters. However, this study provided us knowledge about the adverse effect pattern encountered by Nepalese population suffering from T2DM who were under medication.

CONCLUSION:

Oral hypoglycemic agents may cause various adverse effects in our study. The most common adverse effect seen in diabetic patient was hypoglycemia and majority of them were caused by missing of meal. Even though various side effects were experienced by the patients, very few reported about them to their physician. Also, only few were informed about the adverse effects by their physicians in pre-medication stage and this factor had a significant association with incidence of adverse effects. Physicians can inform patients about the possible adverse effects, which might help patients to cope with unpleasant adverse effects and thus enhance adherence.

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